UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,996	02/18/2005	Hiroyuki Asada	05105/HG	3212

1933 7590 11/17/2010

HOLTZ, HOLTZ, GOODMAN & CHICK PC
220 Fifth Avenue
16TH Floor
NEW YORK, NY 10001-7708

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
11/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HIROYUKI ASADA and AKIO KIMURA

Appeal 2010-009400
Application 10/524,996
Technology Center 1600

Before CAROL A. SPIEGEL, ERIC GRIMES, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134(a) involving claims to ophthalmic solutions comprising latanoprost and ε-aminocaproic acid. The

---

[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

Patent Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The invention concerns an opthalmic solution comprising latanoprost, "a prostaglandin-type therapeutic agent for glaucoma." (Spec. 1.)

Claims 6, 8, 10, 12, 14, and 16 are on appeal. Claims 6 and 12 are representative and read as follows:

6. An aqueous ophthalmic solution comprising 0.005% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adding ε-aminocaproic acid to the solution.

12. An aqueous ophthalmic solution comprising 0.005% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adjusting the pH of the solution to 5.0 to 6.25 and adding ε-aminocaproic acid to the solution.

The Examiner rejected all the claims under 35 U.S.C. § 103(a) as unpatentable over Schneider[2] and Kimura.[3]

OBVIOUSNESS

The Issue

The Examiner's position is that Schneider taught an ophthalmic solution comprising a prostaglandin, such as latanoprost, at 0.001 to 0.005% w/v and having a pH of 6 +/- 0.2. (Ans. 3.) The Examiner found that Schneider recognized that prostaglandins are generally unstable and taught the use of polyethoxylated castor oils as a stabilizing agent. (*Id.*) The

[2] US Patent No. 6,011,062 issued to L. Wayne Schneider et al., Jan. 4, 2000.
[3] US Patent No. 5,556,848 issued to Motoko Kimura et al., Sep. 17, 1996.

Examiner found that Schneider differed from the instant claims by not teaching the addition of ε-aminocaproic acid to its composition. (*Id.* at 4.)

The Examiner found that Kimura taught an ophthalmic suspension comprising difluprednate as the active ingredient and taught adding acetates or ε-aminocaproic acid to its ophthalmic suspension. (*Id.*) According to the Examiner, Kimura taught that these additives suppress formation of agglomerates, prevent lowering of pH, and provide a suspension superior in redispersability and stability. (*Id.*) The Examiner found that Kimura taught that polyoxyethylene castor oils are also useful for these same functions. (*Id.*)

The Examiner reasoned that "[b]ecause Schneider recognized the stability problems of prostaglandins, it would have been obvious to a person having ordinary skill in art at the time of applicants' invention to add a known stabilizing agent such as ε-aminocaproic acid at 0.01-2.0 w/v% to the composition of Schneider...." (*Id.*) According to the Examiner, the skilled artisan would have been motivated by Kimura's teaching that ε-aminocaproic acid beneficially suppresses formation of agglomerates, prevents lowering of pH, and provides a suspension superior in redispersability and stability. (*Id.*)

Appellants challenge the Examiner's rejection by asserting differences between each prior art reference and the claimed invention. Specifically, Appellants assert that Schneider disclosed castor oil to stabilize latanoprost, while the instant claims use ε-aminocaproic acid to stabilize latanoprost and that these stabilizing agents "completely differ in their chemical structure and their chemical properties." (App. Br. 7.) Additionally, Appellants assert that Kimura was directed to "enhancing the dispersion stability" in an

ophthalmic suspension comprising a water-insoluble active ingredient, difluprednate, while the instant claims are directed to "enhancing the chemical stability" of a completely different active ingredient, latanoprost, in a water-soluble ophthalmic solution. (*Id.* at 8-9.) Moreover, Appellants assert that Kimura did not teach or suggest enhancing the chemical stability of latanoprost or any active ingredient, in a water-soluble ophthalmic solution, nor did Kimura teach that ε-aminocaproic acid would increase the chemical stability of an active ingredient. (*Id.* at 9; Reply Br. 3-5.)

Appellants then contend that a skilled artisan would have "no reason for substituting the active ingredient in Schneider et al. (a prostaglandin) for the active ingredient in Kimura et al. (difluprednate), since these two active ingredients are totally different." (App. Br. 10.) Appellants additionally contend that a skilled artisan "would not consider to employ ε-aminocaproic acid as a substitute for the polyethoxylated castor oils employed by Schneider et al." because Kimura disclosed "ε-aminocaproic acid only as an additional component, namely, a buffer." (*Id.*)

Further, Appellants assert that the Specification provides evidence of unexpected results relating to: (a) increased stability of latanoprost in a solution comprising ε-aminocaproic acid, with respect to all of the rejected claims; and (b) improved stability of latanoprost in a solution having a pH of 5 to 6.25, with respect to claims 12, 14 and 16. (*Id.* at 10-14.)

The issues with respect to this rejection are: whether the record supports the Examiner's conclusion that the combined references would have made the claimed ophthalmic solutions prima facie obvious, and if so, whether Appellants have provided evidence of unexpected results such that the totality of evidence weighs in favor of nonobviousness.

Findings of Fact

1. We agree with the Examiner's explicit findings regarding the scope and content of the prior art references. (*See* Ans. 3-5.)

2. Schneider disclosed that its compositions may further comprise various formulary ingredients, including buffers in an amount between about 0.001 and about 1 wt %. (Schneider col. 7, ll. 10-13, 30-31.)

3. Schneider disclosed an exemplary formulation of its composition comprising sodium acetate in an amount of 0.07% and having a pH of 5. (*Id.* at col. 8, ll. 1-15.)

4. Kimura disclosed acetates, particularly sodium acetate, and ε-aminocaproic acid as the preferable buffers that may be included in its compositions. (Kimura col. 3, ll. 19-32.)

5. The Specification describes studying the effects of various additives, including ε-aminocaproic acid, on stability of latanoprost by adding 100 ml of an aqueous solution (pH 7) to 5 mg of latanoprost and then storing samples of the mixture in an incubator at either 50°C or 80°C. (Spec. 13.)

6. The Specification disclosed that in the case of storage at 50°C and at 80°C, the residual ratio, i.e., stabilization effect, was higher in formulations containing ε-aminocaproic acid as compared to formulation containing other additives, not including sodium acetate. (*Id.* at 15 and 16, Table 3.)

7. The Specification describes an experiment in which latanoprost was dissolved in a phosphate buffer having a pH of 4.0, 5.0, 5.5, 6.0, 6.25, 6.5, 6.7, and 8.0 and then stored at either 60°C or 70°C. (*Id.* at 8.)

8. The Specification disclosed that "in the case of storage at 60°C, residual ratios of 95% or higher, namely stable samples, were in the range of pH 5.0 to 6.25. Similarly in the case of storage at 70°C, residual ratios of

90% or higher, namely stable samples, were also in the range of pH of 5.0 to 6.25." (*Id.* at 8 and 10, Table 1.)

9. The Specification states, "From the above-mentioned results, it was found that when pH of the latanoprost ophthalmic solution is adjusted to 5.0 to 6.25, latanoprost is stabilized, and the opthalmic solution can be stored at room temperature." (*Id.* at 9.)

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007). "Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982).

It is well settled that unexpected results must be established by factual evidence. *In re Lindner,* 457 F.2d 506, 508 (CCPA 1972). Additionally, "the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006).

Analysis

A. Prima Facie Obviousness

We are not persuaded by Appellants' contentions. While we agree with Appellants that differences exist between each of the individual prior art references and the claimed invention (*see* App. Br. 7-9), the Examiner rejected the claims over a combination of the two references. Their combined teachings, not the separate teachings, serves as the basis of comparison to the claimed invention. The Examiner combined Schneider's shelf stable aqueous pH 6 ophthalmic solution comprising latanoprost 0.005

w/v% with Kimura's ε-aminocaproic acid, which yields the claimed composition.

Appellants assert that differences between Schneider and Kimura support their contention that the Examiner's combination would not have been obvious. In particular, Appellants contend that a skilled artisan would not consider (a) substituting Schneider's prostaglandin for Kimura's difluprednate, or (b) substituting Schneider's castor oil for Kimura's ε-aminocaproic acid. (App. Br. 10; Reply Br. 2.) However, the Examiner's combination did not involve either of these substitutions. Rather, the Examiner explained that it would have been obvious "to add" Kimura's ε-aminocaproic acid to Schneider's ophthalmic solution comprising latanoprost and castor oil. (Ans. 4.) The inclusion of castor oil in this combination is not beyond the scope of the claims which broadly recite an aqueous composition using the open claim language "comprising."

To the extent Appellants contend (Reply Br. 3-5) that Kimura did not "teach that ε-aminocaproic acid can increase the chemical stability of active ingredients," e.g., Kimura's difluprednate or Schneider's latanoprost, we agree. We also agree that Kimura disclosed the stabilizing effectiveness of ε-aminocaproic acid with respect to a suspension. However, these facts do not establish nonobviousness. As the Examiner explained, the references provide a further basis of prima facie obviousness. (Ans. 6.) Specifically, Schneider disclosed that its ophthalmic formulation may additionally comprise a buffer, including sodium acetate. (Ans. 5; FF-2, 3.) Kimura also disclosed adding a buffer to its composition, preferably sodium acetate or ε-aminocaproic acid. (Ans. 5, FF-4.)

The Examiner reasoned that a skilled artisan would have found it obvious to add ε-aminocaproic acid as the buffer in Schneider's composition instead of sodium acetate because Kimura disclosed sodium acetate and ε-aminocaproic acid as equivalent buffers. (Ans. 5-6.) This reasoning is sound. *See Fout*, 675 F.2d at 301; *KSR,* 550 U.S. at 416. Moreover, Appellants have not challenged this reasoning in their Reply. (*See* Reply 1-10.)

B. Asserted Unexpected Results

Appellants contend that Table 3 in the Specification "shows that after storage at 50°C for 8 weeks, the residual ratio of the latanoprost in an ophthalmic solution is 93.1% when ε-aminocaproic acid is added to the solution." (App. Br. 10.) Additionally, Appellants assert that Table 3 shows that after storage at 80°C for 4 weeks, the residual ratio of the latanoprost is 51.8% when ε-aminocaproic acid is added," compared to 6.3-28.9% when it is not added. (*Id.* 10-11.) Therefore, according to Appellants, "Table 3 clearly shows the stability of latanoprost in an aqueous ophthalmic solution is significantly improved when ε-aminocaproic acid, out of numerous additives, is added." (*Id.* at 11.) However, the "numerous additives" tested in the Specification study did not include sodium acetate, the buffer additive used in the latanoprost composition disclosed in Schneider, and described as an equivalent buffer to ε-aminocaproic acid by Kimura. (FF 3-6.) Thus, Appellants have not shown that their results were unexpected compared to the closest prior art, as required to overcome prima facie obviousness. *See Kao Corp.*, 441 F.3d at 970.

Regarding claims 12, 14, and 16, Appellants further assert that Table 1 in the Specification provides "[u]nexpected results for employing a pH

range of 5.0 to 6.25" by demonstrating that "the stability of latanoprost (residual ratio %) after storage for 28 days at 60°C and 70°C is substantially better at a pH of 5.0 to 6.25, compared to at a pH of each of 4.0, 6.7 and 8.0." (App. Br. 13.) However, Schneider disclosed that its shelf stable latanoprost compositions had a pH of 6 +/- 0.2, which pH falls within the instantly claimed and tested range. (*See* Ans. 3; *see also* FF-7, 8, 9.) Thus, again, Appellants have not established that these results were unexpected over, or even different than, the closest prior art so as to overcome prima facie obviousness.

CONCLUSIONS OF LAW

The record supports the Examiner's conclusion that the combined references would have made the claimed ophthalmic solutions prima facie obvious. Appellants have not provided evidence of unexpected results such that the totality of evidence weighs in favor of nonobviousness.

SUMMARY

We affirm the rejection of claims 6, 8, 10, 12, 14, and 16 under 35 U.S.C. § 103(a) as unpatentable over Schneider and Kimura.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

lp

Appeal 2010-009400
Application 10/524,996

HOLTZ, HOLTZ, GOODMAN & CHICK PC
220 FIFTH AVENUE
16TH FLOOR
NEW YORK NY 10001-7708